

Name: Shahrdad Lotfipour

Email: shahrdad@uci.edu

Functional Role of a Human 3'UTR Alpha6 Nicotinic Receptor Polymorphism (rs2304297) in Adolescent Substance Use

Diana Carreno¹, Anjelica Cardenas¹, Frances, Leslie¹, Shahrdad Lotfipour^{1,2,3}

¹Pharmaceutical Sciences; ²Emergency Medicine; ³Pathology & Laboratory Medicine, UC Irvine

The use of nicotine and tobacco products is a major public health concern, given a recent exponential rise in electronic cigarette use among teens. Since adolescent nicotine exposure can enhance drug consumption later in life, it is especially important to study the molecular mechanisms mediating adolescent nicotine use. Large-scale human candidate gene studies reveal that a common genetic variant of the alpha6 nicotinic acetylcholine receptor (nAChR) subunit (encoded by the CHRNA6 gene, rs2304297) plays a role in adolescent nicotine/tobacco use. The corresponding alpha6 nAChR protein is present in dopamine reward neurons in the brain, suggesting that modifications in its quantity and/or function may influence nicotine effects on addiction-related neurocircuitry. To test this hypothesis, we have engineered a mutant rat line that replicates the genetic variation found in humans. The entire human 3'UTR, with a 'C' to 'G' single nucleotide change in the 123 position, was introduced into Sprague Dawley rats (alpha6 CC and alpha6 GG-carriers), and found to yield functional sex-dependent behavioral results. Rigorously collected behavioral data from this new rat line confirms that the alpha6 3'UTR SNP can modify nicotine-induced behaviors in adolescent alpha6 GG carriers as compared with alpha6 CC carriers, with opposite sex-dependent effects. Our published findings support prior clinical and preclinical data and provide evidence for a new translational animal model to study adolescent substance use. Understanding the role of CHRNA6 3'UTRC123G variations in adolescent nicotine addiction is increasingly important as teen vaping has escalated dramatically, and may lead to improved prevention and intervention strategies.